



Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Panel's Recommendations

- Families traveling to malaria-endemic countries should receive pre-travel counseling, including information on insecticide-treated bed nets, N,N-Diethyl-meta-toluamide, and country-specific antimalarial prophylaxis **(AII)**.
- Trimethoprim-sulfamethoxazole is not recommended for antimalarial prophylaxis **(AIII)**.
- Treatment of malaria is based on disease severity, patient age, parasite species, pregnancy status, and local resistance patterns where the malaria infection was acquired **(AI)**.
- The choice of malaria therapy is not affected by HIV status but can be modified based on potential interactions between antiretroviral and antimalarial drugs **(AIII)**. Quinidine is not recommended for patients who are taking ritonavir **(AIII)** (ritonavir may be replaced if quinidine is needed for severe malaria) and should be administered with caution with atazanavir, darunavir and fosamprenavir **(AIII)**.
- The treatment options for uncomplicated chloroquine-susceptible *Plasmodium falciparum* malaria include chloroquine phosphate, atovaquone-proguanil, artemether-lumefantrine, and quinine sulfate plus either doxycycline, tetracycline (in children aged ≥ 8 years), or clindamycin. Mefloquine is considered an alternative regimen **(AIII)**.
- Chloroquine should not be used to treat malaria infections acquired in areas with chloroquine resistance **(AIII)**.
- Treatment of uncomplicated chloroquine-resistant malaria may include atovaquone-proguanil, quinine sulfate plus either doxycycline or tetracycline (specifically in children aged ≥ 8 years) or clindamycin or artemether-lumefantrine **(AIII)**.
- Treat for presumptive chloroquine-resistant *P. falciparum* malaria in symptomatic patients who have traveled to a region with chloroquine-resistant *P. falciparum* and for whom reliable identification of the malaria species is not possible or who are severely ill **(AIII)**.
- After initial treatment for *Plasmodium vivax* and *Plasmodium ovale* (same as for uncomplicated *P. falciparum*), primaquine is recommended for treatment of the dormant liver stage (hypnozoites) **(AIII)**.
- Glucose-6-phosphate dehydrogenase deficiency must be excluded before use of primaquine because of risk of severe hemolytic anemia **(AIII)**.
- Treatment of severe malaria includes both IV quinidine gluconate plus either doxycycline **OR** clindamycin **OR** tetracycline. Alternatives include artesunate IV (under Investigational New Drug protocol: Contact the Centers for Disease Control and Prevention Malaria Hotline at (770) 488-7788) followed by either doxycycline **OR** atovaquone-proguanil **OR** mefloquine **OR** clindamycin **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Malaria is caused by the obligate, intracellular protozoa of the genus *Plasmodium*, and is transmitted by the bite of an infective female Anopheles mosquito. Worldwide, malaria is a leading killer of children and pregnant women. In the United States, most malaria cases occur in patients who have returned from travels to areas of endemic malaria transmission. Rarely, cases occur as a result of exposure to infected blood products, local mosquito-borne transmission (i.e., autochthonous transmission), or mother-to-child transmission (MTCT) (congenital malaria). Prompt recognition and treatment are essential, and failure to act quickly and appropriately can have grave consequences.

In 2009, 1484 cases of malaria were reported in the United States, of which 4 were fatal.¹ In the majority of cases in which species were identified, *Plasmodium falciparum* was the pathogen involved; however, in 38% of cases, the species was either not reported or unidentified. Lack of adherence to prophylaxis is the key identified risk factor for acquisition of malaria in those for whom data are available.

High-Risk Groups

United States-born children visiting family in malaria-endemic regions are at highest risk of malaria infection. Children of foreign citizenship, children of unknown resident status, and adopted children who come from countries of endemic malaria transmission are also at high risk. Education regarding the misconception that prior exposure to malaria confers protection against re-infection is important; families should be prepared (with malaria chemoprophylaxis) and educated with travel advice (e.g., such as recommending use of insecticide-treated nets and insect repellants) before returning to endemic areas (**AII**). Although some parents may assume that their children are protected from disease because of their ethnic background (from high malaria endemic countries),^{2,3,4} the converse is true, with patients in this group at high risk because of factors such as visiting private residences, sleeping in homes that lack screens or air conditioning, and having longer visits, all of which contribute to a higher risk of contracting malaria (<http://www.cdc.gov/malaria/travelers/vfr.html>). Adults living in the United States but born in malaria-endemic areas often believe they are not susceptible to malaria because of naturally acquired immunity. Such acquired immunity develops after age 5 years in people who reside in areas of stable malaria transmission, but it is partial (providing relative protection against disease, not infection), wanes quickly once people are no longer living in malaria-endemic areas, and may not be present in HIV-infected populations with advanced immunodeficiency. Therefore, both adults and children living in the United States who were born in malaria-endemic areas should be prescribed the same prophylaxis as any other patients traveling to malaria-endemic areas.

Prevention Recommendations

Recommendations for preventing exposure and for primary chemoprophylaxis are identical for HIV-infected and HIV-uninfected individuals (see <http://www.cdc.gov/malaria/travelers/index.html>). All travelers to malaria-endemic regions should receive pre-travel counseling on appropriate chemoprophylaxis and avoidance of mosquitos (**AII**).^{4,5} Families should be counseled regarding signs and symptoms of malaria and the need for early medical intervention if these signs and symptoms are present. An early appropriate medical evaluation should be completed on all patients returning from a malaria-endemic area who have unexplained fever or other signs or symptoms of malaria.

Preventing Exposure

All travelers should use personal protective measures to prevent mosquito bites when traveling to malaria-endemic areas (**AII**),⁶ including sleeping under an insecticide-treated bed net and wearing clothing impregnated with permethrin (effective for weeks and through several washings, but not dry cleaning). Discussions regarding the routine use of bed nets should be individualized as per specific sleeping arrangements (air-conditioned hotel vs. open windows). Long-acting N,N-Diethyl-meta-toluamide (DEET) mosquito repellents are safe, practical, and effective, and the duration of protection increases with increasing DEET concentrations, plateauing between 30% and 50%. DEET should be applied (by patients or their caregivers when appropriate) to skin, but not to wounds, cuts, irritated areas, the mouth, or hands of young children (**AIII**). Additional information about other recommended mosquito repellants can be found at http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm.

Depending on the level of risk, it may be appropriate to recommend to travelers no specific interventions, mosquito-avoidance measures only, or mosquito-avoidance measures plus chemoprophylaxis (Centers for Disease Control and Prevention [CDC] Yellow book; <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm>). Pregnant women should discuss travel to endemic areas with a travel medicine expert.

Primary Chemoprophylaxis

Primary chemoprophylaxis should be prescribed to all individuals traveling to malaria-endemic areas, regardless of ethnicity or prior exposure to or illness with malaria. Antimalarial medications may need special preparation, and some are not easily delivered to children. Therefore, families planning to travel to malaria-endemic areas are advised to visit a travel medicine specialist with training and experience in pediatrics at least 2 weeks before departure **(AII)**. If that is not possible, families can still see a travel medicine specialist up to the day of departure, because some antimalarial prophylaxis regimens can still be prescribed and effectively used even at that late date.

For patients traveling to areas with chloroquine-sensitive malaria, chloroquine phosphate (5 mg/kg body weight base, up to 300-mg base) given once weekly is acceptable. Other acceptable choices include primaquine, atovaquone/proguanil, doxycycline, and mefloquine. For travelers to areas with mainly *Plasmodium vivax*, primaquine is a very good option. Travellers who will be given primaquine should have glucose-6-phosphate dehydrogenase (G6PD) testing before this medication is started. Travelers to areas with chloroquine-resistant malaria should take atovaquone/proguanil daily (dosed on a sliding scale by weight bands), or daily doxycycline (2.2 mg/kg body weight for children aged ≥ 8 years) or weekly mefloquine, dosed based on weight. Medications for prophylaxis should be started before leaving and continued after returning from travel, as per their specific schedule. Trimethoprim-sulfamethoxazole (TMP-SMX) is not a surrogate for antimalarial prophylaxis, and **is not recommended** as effective prophylaxis for malaria **(AIII)**. Although TMP-SMX prophylaxis appears to reduce episodes of clinical malaria to varying degrees, with the already almost universal resistance to sulfadoxine pyrimethamine, it is extremely unlikely that TMP-SMX would be useful alone as primary prophylaxis.⁷

Discontinuing Primary Prophylaxis

Travel-related chemoprophylaxis with chloroquine, mefloquine, or doxycycline usually should be continued for 4 weeks after departure from a malaria-endemic area because these drugs are not effective against malarial parasites developing in the liver and kill the parasite only once it has emerged to infect the red blood cells. Atovaquone-proguanil and primaquine may be discontinued 1 week after departure from malaria-endemic areas.

Clinical and Laboratory Manifestations

HIV increases the frequency and severity of clinical malaria episodes in more severely immunosuppressed adults, pregnant women, and older children, possibly reflecting HIV-mediated interference with acquisition of malaria immunity, but not related to failure of initial antimalarial therapy.^{7,8} In young children, there is no clear evidence that HIV infection is associated with more severe malaria disease, although one case-control study in Uganda found an association between HIV infection and cerebral malaria in children.⁹

In a case series of returning travelers, symptoms most commonly reported include fever (100%), headache (100%), weakness (94%), profuse night sweats (91%), insomnia (69%), arthralgias (59%), myalgias (56%), diarrhea (13%), and abdominal cramps (8%).¹⁰ Patients may also have pallor, hepatosplenomegaly, or jaundice. Altered consciousness or seizures may indicate progression to severe malaria. Splenic rupture can be a rare presentation of malaria, requiring urgent medical and surgical management. Rash, lymphadenopathy, and signs of pulmonary consolidation are not characteristic of malaria. Laboratory values may include anemia; high, normal, or low neutrophil counts; normal or low platelets; low sodium (usually because of syndrome of inappropriate antidiuretic hormone secretion and/or dehydration); lactic acidosis; renal insufficiency, increased creatinine, proteinuria, and hemoglobinuria; and elevated lactate dehydrogenase.^{11,12} Severe malaria may present before severe anemia (hemoglobin < 7 g/dL) is documented.

Although fever is often the most common clinical presentation of malaria in people coming from areas of endemic malaria transmission, it is not uniformly present in children. Non-specific clinical findings often predominate in children and clinical diagnosis in them can be difficult. Malaria fever patterns in children also

often do not follow the classically described tertian or quartan patterns described in adults.^{13,14} Children more often present with hepatomegaly, jaundice, or splenomegaly than do adults. They are also more likely to have fever >40°C and may present with febrile convulsions. Laboratory findings may include low serum glucose (seen with falciparum malaria), whereas serum glucose measurements in adults may be normal. Children who have severe malaria also may have concomitant bacteremia/sepsis.^{2,11,12} In returning travelers, when children are diagnosed with malaria, their siblings might present with malaria at the same time.²

Splenomegaly, fever, and thrombocytopenia are highly specific for malaria in immigrant children and need appropriate evaluation.^{13,15} Congenital malaria is rare but should be considered in febrile neonates whose mothers migrated from areas where malaria is endemic; however, empiric therapy should not be administered without a confirmed diagnosis.¹³ HIV/malaria coinfection during pregnancy has been shown to have additional detrimental effects on maternal and infant survival and to confer increased risk of MTCT of both HIV and malaria.¹⁶

Diagnosis

For early and prompt recognition of malaria, physicians must obtain a complete travel history from every febrile patient and maintain a high index of suspicion for malaria in travelers returning from areas of endemic malaria, remembering that signs and symptoms also can vary depending on chemoprophylaxis and prior partial treatment for malaria (see Table 7 from¹⁷ for list of resources or <http://wwwnc.cdc.gov/travel/destinations/list.htm>). Children who have recently migrated from regions where malaria is endemic should be evaluated for malarial infection upon arrival and/or if they become ill after arriving in the United States. A Giemsa-stained thick blood smear is the most sensitive smear technique for detecting infection, whereas a thin blood smear is used for determination of parasite species and burden (for an example of malaria parasites on smear, please visit http://www.dpd.cdc.gov/dpdx/HTML/Image_Library.htm). Smear accuracy depends upon proper preparation and interpretation of thick and thin smears by experienced laboratory personnel.¹⁷ Because symptoms can develop before parasitemia is detectable in a non-immune person, the initial blood-smear examination may be misleadingly negative. Blood smears should be obtained every 12 to 24 hours for a total of 3 sets to fully evaluate for malaria; if all 3 sets are negative, the probability of malaria is extremely low. In all patients in whom malaria is suspected, smears should be read immediately. A qualified person who can perform and read smears should always be available, even at off-hours. Every effort should be made to establish a diagnosis before therapy is initiated. However, if severe malaria is strongly suspected and diagnostic interpretation is not readily available, empiric intravenous therapy for presumed *P. falciparum* infection should be initiated, with a blood smear preserved for reading as soon as possible. Consultation and aid in the initial diagnosis, speciation, and treatment plan is available via the CDC Malaria Hotline at (770) 488-7788 (Monday–Friday, 9 a.m.–5 p.m., eastern time. For emergency consultation after hours, call (770) 488-7100, and ask to speak with a CDC Malaria Branch clinician).

Performance of rapid diagnostic tests (RDTs) varies greatly, and only one test (Binax) currently is Food and Drug Administration (FDA)-approved. Such tests may have limited usefulness early in infection because their sensitivity is decreased with lower parasite density (see http://www.wpro.who.int/sites/rdt/who_rdt_evaluation/). However, if microscopy is not immediately available, these tests can be used to aid in establishing a diagnosis of malaria. Microscopy must still be performed on all suspected cases of malaria, despite positive and negative RDTs, for confirmation.

Malaria in the United States is a reportable disease. Directions on case definitions and reporting can be found at <http://www.cdc.gov/malaria/report.html>.

Treating Disease

Chemoprophylaxis is not completely effective, and malaria should be included in the differential diagnosis of fever or other signs or symptoms consistent with malaria in anyone who traveled to malaria-endemic areas

during the previous 12 months (see <http://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/malaria-guidelines-overseas.html#sect2>). Malaria medications purchased in sub-Saharan Africa or Southeast Asia may be counterfeit; therefore, the index of suspicion must remain high when evaluating children with fever coming from endemic areas, regardless of prior history of antimalarial therapy.

CDC recommends presumptive treatment for malaria for all refugees and adoptees resettling to the United States from sub-Saharan Africa, including those who were treated for malaria before departing from Africa but who did not receive primaquine for treatment of dormant liver stage forms (hypnozoites) of *Plasmodium ovale* and *P. vivax* infection. These patients remain at risk of developing malaria after arrival in the United States and should be evaluated with a high index of suspicion for malaria. Children with past or current *P. vivax* or *P. ovale* infection should receive treatment with primaquine to eradicate the dormant liver stage, if the drug was not previously administered (see CDC Guidance located at <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>).

Treatment of malaria is based on the disease severity, patient age at onset, parasite species, pregnancy status, and known resistance patterns in the area where the malaria infection was acquired (**AI**). Drug dosing for pediatric patients must be adjusted for weight, and dosing should never exceed the recommended adult dose. Recommendations for treatment—including drug dosing in HIV-infected children and adolescents with malaria—by species are described below and summarized in [Table 1](#), and can also be found at http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Additional information can be found at <http://www.malaria.org/ABOUT%20MALARIA/Treatment%20of%20Malaria-Guidelines%20for%20clinicians%20WHO.pdf> for further clinical guidance.

HIV infection status does not affect choice or dosing of antimalarial therapy. However, choice of antimalarial therapy may be affected by interactions between antiretroviral (ARV) and antimalarial drugs; clinicians are urged to evaluate for drug interactions before initiating antimalarial therapy (please see Drug Interactions section below).

Unknown Species

Clinicians should always treat patients who traveled to a region in which chloroquine-resistant *P. falciparum* malaria is present for chloroquine-resistant *P. falciparum* malaria if reliable identification of the malaria species is not possible or the patient is severely ill (**AIII**).

Uncomplicated Malaria

Uncomplicated malaria is defined by the World Health Organization as “symptomatic infection with malaria parasitemia without signs of severity and/or evidence of vital organ dysfunction.”¹⁸ The preferred treatment options for uncomplicated malaria include chloroquine phosphate (if chloroquine-susceptible), atovaquone-proguanil, artemether-lumefantrine, or quinine sulfate plus a second medicine (either tetracycline, doxycycline [in children aged ≥8 years] or clindamycin) (see Dosing Table for details) (**AI**). Mefloquine also can be used for treatment, but has a higher rate of side effects (**AIII**). Primaquine also must be administered for radical cure of *P. vivax* and *P. ovale* infection. G6PD deficiency **must** be excluded before first use of primaquine because of the risk of severe hemolytic anemia. Primaquine should not be used in pregnant women because the presence of G6PD deficiency cannot be determined in the unborn child (**AIII**).

Severe Malaria

Severe malaria is defined as acute malaria “with signs of severity and/or evidence of vital organ dysfunction”¹⁸ and is most often caused by *P. falciparum*, but can also be caused by *P. vivax*. Mixed infections can also occur. These signs, symptoms, and laboratory parameters include diminished consciousness or seizures, respiratory distress (acute respiratory distress syndrome [ARDS], Kussmaul’s respiration), prostration, hyperparasitemia (>5%), severe anemia (hemoglobin <7 g/dL), hypoglycemia, jaundice/icterus, renal insufficiency, hemoglobinuria, shock, cessation of eating and drinking, repetitive vomiting, or hyperpyrexia. Cerebral malaria is usually defined by presence of coma (Glasgow coma scale

<11, Blantyre coma scale <3). Severe malaria can present long before hemoglobin goes below the 7 mg/dL threshold because of the hemo-concentrating effects of dehydration.

Patients diagnosed with severe malaria should be treated aggressively with intravenous (IV) antimalarial therapy. The only FDA-approved regimen includes quinidine gluconate plus one of the following: doxycycline, tetracycline, or clindamycin. A promising¹⁹ alternative parenteral therapy is IV artesunate (available under Investigational New Drug protocol from CDC for certain patients meeting criteria). Additional alternative therapies include atovaquone-proguanil, clindamycin, mefloquine, or (for children aged ≥ 8 years) doxycycline. Treatment with IV quinidine or artesunate should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria treated with quinidine should be given an IV loading dose unless they have received more than 40 mg/kg body weight of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine because of the known complications of quinidine, including widening of the QRS complex and/or lengthening of the QTc interval. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the IV infusion. IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout it.

Exchange transfusion should be considered (**BII**) only for treatment of very severe malaria when children have a parasite density of more than 10% and if complications such as cerebral malaria, ARDS or renal complications exist. The risks of exchange transfusion include fluid overload, febrile and allergic reactions, metabolic disturbances (e.g., hypocalcaemia), red blood cell alloantibody sensitization, blood-borne transmissible infection, and line sepsis.²⁰⁻²² The parasite density should be monitored every 12 hours until it falls below 1%, which usually requires the exchange of 8 to 10 units of blood in adults.

Malaria Despite Chemoprophylaxis

Medication used for chemoprophylaxis should not be used as a part of a new treatment regimen in individuals who develop malaria despite taking chemoprophylaxis; rather, treatment with one of the other options is recommended.

Drug Interactions

There are multiple potential interactions between ARV and antimalarial drugs, but data from HIV-infected children and adults remain limited.^{7,23-25} Many antimalarials are metabolized by cytochrome p450 enzymes, while certain non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) either inhibit or induce cytochrome p450 enzymes.²⁶⁻²⁸ Tetracyclines have no clinically significant interactions expected with PIs or NNRTIs. Atovaquone is not expected to have any significant interaction with common nucleoside reverse transcriptase inhibitors, although no data are available for proguanil. Ritonavir inhibits quinidine metabolism; therefore, concomitant administration of ritonavir (including co-formulated products like lopinavir/ritonavir that contain ritonavir) and quinidine is not recommended. Replacement of ritonavir in ritonavir-containing cART should be considered. The inhibitory action of ritonavir will still be present for several days after dosing is interrupted; thus, in patients with severe malaria already on ritonavir, artesunate should be considered. Caution is also advised before co-administering quinidine with other PIs (including atazanavir, darunavir, and fosamprenavir).

Other drug-drug interactions exist but have not been studied. The CDC Malaria Hotline is an excellent resource for additional assistance with drug-drug interactions, as are the World Health Organization's Guidelines for the Treatment of Malaria (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf). An interactive web-based resource for checking on drug interactions involving ARV drugs is found at the University of Liverpool website <http://www.hiv-druginteractions.org>.

Potential Clinically Relevant Interactions between Antimalarial and Antiretroviral Drugs*

Antimalarial Drug	Protease Inhibitors	NRTI	NNRTI
Quinine	<u>PIs</u> : increase quinine levels	No available data	<u>Efavirenz, Nevirapine</u> : reduces quinine levels
Atovaquone/Proguanil	<u>Lopinavir/Ritonavir, Atazanavir/Ritonavir</u> : reduces atovaquone and proguanil levels		<u>Efavirenz</u> : reduces atovaquone and proguanil levels
Mefloquine	<u>Ritonavir</u> : reduces ritonavir levels		<u>Efavirenz, Nevirapine</u> : reduces mefloquine levels
Lumefantrine, Halofantrine	<u>PIs</u> : increase lumefantrine or halofantrine levels, which can prolong QT interval		<u>Efavirenz, Nevirapine</u> : increases lumefantrine or halofantrine levels, which can prolong QT interval
Amodiaquine plus Artesunate			<u>Efavirenz</u> : increases amodiaquine concentration which can increase hepatic toxicity; do not co-administer
Chloroquine, Pyrimethamine, Sulfadoxine-Pyrimethamine	<u>Ritonavir</u> : alters anti-malarial drug metabolism, may increase chloroquine levels		
Sulfadoxine-Pyrimethamine		<u>Zidovudine</u> : possibly increases risk of anemia	<u>Nevirapine</u> : possibly increases adverse skin or liver adverse reactions; do not start both drugs simultaneously
Artemisinin	<u>PIs</u> : alter artemisinin metabolism		<u>Nevirapine</u> : may decrease artemisinin levels
Dapsone	<u>Saquinavir</u> : alters dapsone metabolism		

Key to Acronyms: NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI= protease inhibitor

* Modified from: Flateau, C., G. Le Loup, et al. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect Dis.* 2011. 11(7);541-556.

Special Populations

Because primaquine is not routinely prescribed for immigrants as part of a post-treatment/pre-departure regimen, patients who may have had *P. vivax* or *P. ovale* infection in the past would be at continued risk of developing malaria months to years after arrival in the United States. Presumptive treatment on arrival (preferable) or laboratory screening to detect *Plasmodium* infection is recommended for refugees originating in sub-Saharan Africa who have not received pre-departure therapy with a recommended regimen (see <http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/malaria-guidelines-domestic.html>).

Monitoring and Adverse Events (Including IRIS)

Severe malaria commonly induces hypoglycemia in children, especially when treated with IV quinine/quinidine because of inhibition of gluconeogenesis and induction of endogenous insulin production. Therefore, monitoring glucose levels and use of a glucose-containing crystalloid solution for fluid maintenance is prudent until IV quinine/quinidine therapy has been completed. Monitoring glucose is especially important for children with altered mental status. Cardiac and intensive-care monitoring is also recommended because IV quinine/quinidine can cause hypotension and widening of the QRS interval. Quinine toxicity, a cluster of symptoms that includes tinnitus, dizziness, disorientation, nausea, visual changes, and auditory deficits, can

occur. Many of the adverse events associated with quinine are dose-related, and because of age-related differences in the rate at which quinine is eliminated from the body, the frequency and severity of adverse effects associated with quinine drug products may be lower in children. Tinnitus alone, a common (50%–75%) adverse reaction to both oral and IV quinine, usually resolves after treatment. Use of mefloquine at treatment doses may be associated with neuropsychiatric symptoms. Following antimalarial therapy, HIV-infected children should be monitored closely for hematologic complications (especially anemia and neutropenia), which are more frequent because of both the direct hematologic effects of HIV infection and of HIV treatment with other bone-marrow-suppressive drugs such as TMP-SMX and zidovudine. Immune reconstitution inflammatory syndrome caused by malaria has not been reported.

Managing Treatment Failure

Failure of treatment for *P. falciparum* is uncommon in children who receive a full course of appropriate antimalarial therapy. Patients should be monitored for clinical and laboratory response (thick and thin smear) and for signs of recrudescence after therapy completion. Relapse of *P. vivax* and *P. ovale* can occur from the dormant (hypnozoite) liver form but is less common following primaquine treatment. When treatment failure occurs, malaria speciation should be confirmed, as should the geography of where the malaria was acquired. Retreatment with an appropriate first-line regimen (but not the same regimen as initially used) should be given. Discussion with a Pediatric Infectious Disease specialist or consultation through the CDC malaria hotline is appropriate when complex situations arise.

Preventing Recurrence

Except for re-activation of *P. vivax* and *P. ovale* hypnozoites, malaria once successfully treated does not recur, unless re-exposure and re-infection occur. One or even several episodes of malaria infection does not imply protective immunity, and continued exposure to malaria parasites can result in repeated infection, which should be treated as aggressively as the initial event.

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Dosing Recommendations for Prevention and Treatment of Malaria (page 1 of 3)

Indication	First Choice	Comments/Special Issues
Primary Prophylaxis	<p><u>For Travel To Chloroquine-Sensitive Areas:</u></p> <ul style="list-style-type: none"> Chloroquine base 5 mg/kg body weight base by mouth, up to 300 mg once weekly (equivalent to 7.5 mg/kg body weight chloroquine phosphate). Start 1–2 weeks before leaving, take weekly while away, and then take once weekly for 4 weeks after returning home Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home <ul style="list-style-type: none"> 11–20 kg; 1 pediatric tablet (62.5 mg/25 mg) 21–30 kg; 2 pediatric tablets (125 mg/50 mg) 31–40 kg; 3 pediatric tablets (187.5 mg/75 mg) >40 kg; 1 adult tablet (250 mg/100 mg) Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1–2 days before travel, daily while away, and then up to 4 weeks after returning Mefloquine 5 mg/kg body weight orally given once weekly (max 250 mg) <p><u>For Areas with Mainly <i>P. Vivax</i>:</u></p> <ul style="list-style-type: none"> Primaquine phosphate 0.6 mg/kg body weight base once daily by mouth, up to a maximum of 30 mg base/day. Starting 1 day before leaving, taken daily, and for 3–7 days after return <p><u>For Travel to Chloroquine-Resistant Areas:</u></p> <ul style="list-style-type: none"> Atovaquone/proguanil once daily started 1–2 days before travel, for duration of stay, and then for 1 week after returning home <ul style="list-style-type: none"> 11–20 kg; 1 pediatric tablet (62.5 mg/25 mg) 21–30 kg; 2 pediatric tablets (125 mg/50 mg) 31–40 kg; 3 pediatric tablets (187.5 mg/75 mg) >40 kg; 1 adult tablet (250 mg/100 mg) Doxycycline 2.2 mg/kg body weight (maximum 100 mg) by mouth once daily for children aged ≥8 years. Must be taken 1–2 days before travel, daily while away, and then up to 4 weeks after returning Mefloquine 5 mg/kg body weight orally given once weekly (maximum 250 mg) 	<p>Recommendations are the same for HIV-infected and HIV-uninfected children. Please refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/</p> <p>For travel to chloroquine-sensitive areas. Equally recommended options include chloroquine, atovaquone/proguanil, doxycycline (for children aged ≥8 years), and mefloquine; primaquine is recommended for areas with mainly <i>P. vivax</i>.</p> <p>G6PD screening must be performed prior to primaquine use.</p> <p>Chloroquine phosphate is the only formulation of chloroquine available in the United States; 10 mg of chloroquine phosphate = 6 mg of chloroquine base.</p> <p>For travel to chloroquine-resistant areas, preferred drugs are atovaquone/proguanil, doxycycline (for children aged ≥8 years) or mefloquine.</p>

Dosing Recommendations for Prevention and Treatment of Malaria (page 2 of 3)

Indication	First Choice	Comments/Special Issues
Secondary Prophylaxis	<p><u>For <i>P. vivax</i> or <i>P. ovale</i>:</u></p> <ul style="list-style-type: none"> Primaquine 0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily for 14 days after departure from the malarious area 	<p>This regimen, known as PART, is recommended only for individuals who have resided in a malaria-endemic area for an extended period of time. Adult dose: 30 mg base (52.6 mg salt) orally, daily for 14 days after departure from the malarious area.</p> <p>http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#1939</p>
Treatment	<p><u>Uncomplicated <i>P. falciparum</i> or Unknown Malaria Species, from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region:</u></p> <ul style="list-style-type: none"> Atovaquone-proguanil (pediatric tablets 62.5 mg/25 mg; adult tablets 250 mg/100 mg), dosed once daily: <ul style="list-style-type: none"> 5–8 kg; 2 pediatric tablets for 3 days; 9–10 kg; 3 pediatric tablets for 3 days; 11–20 kg; 4 pediatric tablets or 1 adult tablet for 3 days; 21–30 kg; 2 adult tablets for 3 days; 31–40 kg; 3 adult tablets for 3 days; >40 kg; 4 adult tablets for 3 days <p><u>Uncomplicated <i>P. falciparum</i> OR Unknown Malaria Species From Chloroquine-Sensitive Region (See Comments for Link to Resistance Map):</u></p> <ul style="list-style-type: none"> Chloroquine phosphate: 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2500 mg] = 25 mg/kg body weight chloroquine base) <p><u><i>P. vivax</i>, <i>P. ovale</i>, <i>P. malariae</i>, <i>P. knowlesi</i> (All Areas Except Papua New Guinea, Indonesia; See Comments)</u></p> <p><u>Initial Therapy (Followed by Anti-Relapse Therapy for <i>P. ovale</i> and <i>P. Vivax</i>):</u></p> <ul style="list-style-type: none"> Chloroquine phosphate 16.6 mg/kg body weight (10 mg/kg body weight chloroquine base) (maximum 1000 mg) by mouth once, then 8.3 mg/kg body weight (maximum 500 mg) by mouth at 6, 24, and 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [maximum 2500 mg] = 25 mg/kg body weight chloroquine base) <p><u>Anti-Relapse Therapy for <i>P. ovale</i>, <i>P. vivax</i>:</u></p> <ul style="list-style-type: none"> Primaquine 0.5 mg base/kg body weight (max 30 mg base) by mouth once daily for 14 days 	<p>For quinine-based regimens, doxycycline or tetracycline should be used only in children aged ≥8 years. An alternative for children aged ≥8 years is clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours. Clindamycin should be used for children aged <8 years.</p> <p>Before primaquine is given, G6PD status must be verified. Primaquine may be given in combination with chloroquine if the G6PD status is known and negative, otherwise give after chloroquine (when G6PD status is available)</p> <p>For most updated prevention and treatment recommendations for specific region, refer to updated CDC treatment table available at http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf</p> <p>For sensitive and resistant malaria map: http://cdc-malaria.ncsa.uiuc.edu/</p> <p>High treatment failure rates due to chloroquine-resistant <i>P. vivax</i> have been documented in Papua New Guinea and Indonesia. Treatment should be selected from one of the three following options:</p> <ul style="list-style-type: none"> Atovaquone-proguanil plus primaquine phosphate Quinine sulfate plus EITHER doxycycline OR tetracycline PLUS primaquine phosphate. This regimen cannot be used in children aged <8 years. Mefloquine plus primaquine phosphate

Dosing Recommendations for Prevention and Treatment of Malaria (page 3 of 3)

Indication	First Choice	Comments/Special Issues
Treatment, continued	<p><u>Uncomplicated <i>P. falciparum</i> or Unknown Malaria Species from Chloroquine-Resistant Areas (All Malaria Areas Except Those Listed as Chloroquine Sensitive) or Unknown Region:</u></p> <ul style="list-style-type: none"> • Mefloquine (250-mg tablets only): 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth given 12 hours later • Quinine sulfate 10 mg/kg body weight (maximum 650 mg) per dose by mouth every 8 hours for 3 to 7 days, plus Clindamycin 7 mg/kg body weight per dose by mouth every 8 hours for 7 days, or doxycycline: 2.2 mg/kg body weight per dose (maximum 100 mg) given by mouth every 12 hours, or tetracycline 6–12.5 mg/kg body weight per dose by mouth given every 6 hours (maximum dose: 500 mg per dose given 4 times daily) for 7 days. • Artemether-lumefantrine: 1 tablet = 20 mg Artemether and 120 mg lumefantrine, a 3-day treatment schedule for a total of 6 doses. The second dose follows the initial dose 8 hours later, then 1 dose twice daily for the next 2 days. <ul style="list-style-type: none"> • 5 to <15 kg; 1 tablet per dose • 15 to <25 kg; 2 tablets per dose • 25 to <35 kg; 3 tablets per dose • >35 kg; 4 tablets per dose 	
Severe Malaria	<ul style="list-style-type: none"> • Quinidine gluconate 10 mg/kg body weight IV loading dose over 1–2 hours, then 0.02 mg/kg body weight/minute infusion for ≥24 hours (Treatment duration: 7 days in Southeast Asia, Oceania, otherwise 3 days) <u>PLUS One of the Following:</u> <ul style="list-style-type: none"> • Doxycycline 100 mg per dose by mouth every 12 hours for 7 days; for children <45 kg, use 2.2 mg/kg body weight per dose OR • Clindamycin 7 mg/kg body weight per dose by mouth given every 8 hours for 7 days. OR • Tetracycline 6–12.5 mg/kg body weight per dose every 6 hours (maximum dose 500 mg per dose given 4 times daily) for 7 days • Artesunate 2.4 mg/kg body weight IV bolus at 0, 12, 24, and 48 hours <u>PLUS One of the Following:</u> <ul style="list-style-type: none"> • Doxycycline (treatment dosing as above), or Atovaquone-proguanil (treatment dosing as above), or • Mefloquine 15 mg/kg body weight (maximum 750 mg) by mouth once, then 10 mg/kg body weight (maximum 500 mg) by mouth once given 12 hours later, or • Clindamycin (dosing as above) 	<p>Quinidine gluconate is a class 1a anti-arrhythmic agent not typically stocked in pediatric hospitals. When regional supplies are unavailable, the CDC Malaria hotline may be of assistance (see below). Do not give quinidine gluconate as an IV bolus. Quinidine gluconate IV should be administered in a monitored setting. Cardiac monitoring required. Adverse events including severe hypoglycemia, prolongation of the QT interval, ventricular arrhythmia, and hypotension can result from the use of this drug at treatment doses.</p> <p>IND: IV artesunate is available from CDC. Contact the CDC Malaria Hotline at (770) 488-7788 from 8 a.m.–4:30 p.m. EST or (770) 488-7100 after hours, weekends, and holidays. Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), clindamycin, mefloquine, or (for children aged >8 years) doxycycline.</p> <p>Quinidine gluconate: 10 mg = 6.25 mg quinidine base.</p> <p>Doxycycline (or tetracycline) should be used in children aged ≥8 years. For patients unable to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline. For children >45 kg, use the same dosing as per adults. For IV use, avoid rapid administration.</p> <p>For patients unable to take oral clindamycin, give 10 mg base/kg loading dose IV, followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as a patient can take oral medication. For IV use, avoid rapid administration.</p> <p><u>Drug Interactions:</u></p> <ul style="list-style-type: none"> • Avoid co-administration of quinidine with ritonavir • Use quinidine with caution with other protease inhibitors.

Key to Acronyms: CDC = Centers for Disease Control and Prevention; G6PD = glucose-6-phosphate dehydrogenase; IND = investigational new drug; IV = intravenous; PART = presumptive anti-relapse therapy